Current Treatment Options in Cardiovascular Medicine (2010) 12:250–260
DOI 10.1007/s11936-010-0069-6

Cerebrovascular Disease and Stroke

Update on Antithrombotic Therapy for Stroke Prevention in Atrial Fibrillation

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Published online: 10 April 2010

Opinion statement

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly, affecting 1 in 20 adults over the age of 70 years. Stroke is a major yet highly preventable complication of AF, and the strokes related to AF often are disabling and fatal. Warfarin is the treatment of choice in high-risk patients with AF, and its superior efficacy over aspirin for preventing stroke in these patients is widely recognized. However, several eligible patients with AF are not being treated with warfarin or are being treated inadequately, largely because of concerns regarding the attendant strict monitoring, drug interactions, and risk of major bleeding. As such, alternative antithrombotic therapies that can rival or exceed the efficacy of warfarin, yet compare favorably with its administration and side effect profile, are being sought. One such strategy, the use of a combination antiplatelet regimen, for stroke prevention in high-risk patients with nonvalvular AF was investigated recently in two clinical trials. This article reviews the role of combination antiplatelet regimens in stroke prevention for patients with AF. Other therapies discussed include oral anticoagulation, single antiplatelet therapies, oral anticoagulation plus antiplatelet treatment, direct thrombin inhibitors, and factor Xa inhibitors.

Introduction

Atrial fibrillation (AF) is characterized by disordered electrical activity in the atria that causes an irregular and often rapid contraction of the ventricles [1]. AF may limit itself, recur (paroxysmal), or be persistent (lasting more than 7 days), and its overall prevalence increases with age, from 0.7% in persons aged 55 to 59 years to 18% in those 85 years and older [2]. The major complication of AF is systemic embolism (accounting for ~50% of all cardiogenic emboli), mostly to the cerebral vascular bed, the latter of which manifests as strokes. After adjustment for other vascular risk factors, AF alone is associated with a three-to fourfold increased risk of stroke, and more than 75,000 cases of AF-related stroke are believed to occur each year in the United States [2]. These strokes generally are larger, more disabling, and more likely to be fatal than strokes of other causes.

Antithrombotic therapy is the cornerstone of stroke prevention among AF patients, and the incidence of

ischemic stroke among patients with AF not treated with antithrombotic agents averages 4% to 5% per year, and may be greater than 13% per year in high-risk patients [3]. Oral anticoagulation, which generally involves the use of warfarin, currently is the treatment of choice for mitigating stroke risk in AF patients, but its use is limited by a narrow therapeutic index that demands strict monitoring, several drug and dietary interactions, a lack of firm caregiver commitment to ensure compliance with treatment and follow-up visits, and the risk of major bleeding, including hemorrhagic stroke [1]. Practitioners also have concerns about physical immobility from age-related health problems leading to falls and hemorrhagic complications, and whether participants in clinical trials, who generally are followed up more closely to ensure adherence to the study protocol, are representative of patients seen in "real-world" practice, who may not necessarily be compliant with management protocols.

All the aforementioned factors have led to suboptimal warfarin use in clinical practice, with as many as 50% of eligible AF patients not receiving it, or up to three quarters not being treated adequately. As a result, various alternative antithrombotic therapies have, and continue to be, actively investigated for stroke prevention in patients with AF. One such regimen is combination antiplatelet therapy. This review article discusses up-to-date evidence-based antithrombotic treatment for stroke prevention in AF patients, with a major emphasis on the role of combination antiplatelet therapy.

Antithrombotic treatment

- Stroke in patients with AF is caused mainly by cardiogenic embolism. Over the years, various clinical trials of antiplatelet and anticoagulant medications to prevent stroke in AF have been conducted with the goal of interrupting the presumed cardioembolic mechanism of stroke in AF. In this section, the results of investigations of pertinent antithrombotic regimens are discussed.

Single antiplatelet therapy (aspirin)

- Aspirin prevents platelet activation by inhibiting the enzyme cyclooxygenase, thereby blocking thromboxane generation. A pooled analysis of individual patient-level data from three trials (Copenhagen Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study [AFASAK] 1; Stroke Prevention in Atrial Fibrillation [SPAF] I; and European Atrial Fibrillation Trial [EAFT]) resulted in an estimated relative risk (RR) reduction of 21% for aspirin compared with placebo (95% CI, 0%–38%) [4]. The confidence intervals for the pooled result indicate that the risk reduction across trials was barely significant. Other meta-analyses of aspirin versus control in AF patients have been conducted at the study level, not the patient level, and suggest a 22% (95% CI, 2%–38%) reduction in the risk of stroke in favor of aspirin [5].

Oral anticoagulation

- Pooled results from primary prevention trials of warfarin versus control have shown the superior efficacy of warfarin, which was consistent across studies, with an overall RR reduction of 68% (95%

CI, 50%–79%) and an absolute reduction in annual stroke rate from 4.5% in the control patients to 1.4% in patients assigned to adjusted-dose warfarin [6]. Overall, warfarin use has been shown to be relatively safe, with an annual rate of major bleeding of 1.3% on warfarin compared with 1% for patients on placebo or aspirin. The optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be 2.0 to 3.0. Data from a large case-control study [7] and clinical trials [8, 9] indicate that the efficacy of oral anticoagulation drops significantly below an international normalized ratio (INR) of 2.0.

- Studies comparing oral anticoagulation directly with aspirin suggest the risk reduction associated with oral anticoagulation therapy is much greater than that provided by aspirin. A meta-analysis of these studies reported a 36% (95% CI, 14%–52%) relative reduction in the risk of all stroke with adjusted-dose oral anticoagulation compared with aspirin and a 46% (95% CI, 27%–60%) reduction in the risk of ischemic stroke [5]. A patient-level meta-analysis found an RR reduction of 46% (95% CI, 29%–57%) for all stroke and 52% (95% CI, 37%–63%) for ischemic stroke with anticoagulation versus aspirin therapy [4]. Major hemorrhage was increased 1.7-fold (95% CI for hazard ratio [HR], 1.21–2.41) (Table 1).

Oral anticoagulation plus antiplatelet therapy

- Because patients with AF often have coexisting atherosclerotic vascular disease, it is thought that both warfarin and aspirin may be necessary to simultaneously prevent thrombus formation in the left atrium and arteries [1]. Combining low-dose oral anticoagulation with aspirin appears to add relatively little protection against stroke compared with aspirin alone in patients with AF, whereas the combination of aspirin and oral anticoagulation at higher intensities significantly boosted the risk of intracranial hemorrhage, especially in elderly patients [10]. However, in the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF), patients were stratified into a higher-risk group

Table 1. Main implications of ACTIVE-A versus prior warfarin data (from meta-analyses)

Effect	Relative risk reduction, % Warfarin vs aspirin (meta-analyses) [20]	Clopidogrel plus aspirin vs aspirin (ACTIVE-A) [14.••]
Reduction in stroke	−38	−28
Increase in intracranial hemorrhages	+128	+87
Increase in extracranial hemorrhages	+70	+51

ACTIVE-A—Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events
(*Adapted from* Stuart J. Connolly, MD; with permission)

(AF and rheumatic mitral stenosis or a history of embolism) and a lower-risk group (AF and age >60 years, hypertension, or heart failure) [11]. The higher-risk patients were randomly assigned to treatment with anticoagulation (INR 1.4–2.4) combined with the platelet cyclooxygenase inhibitor triflusal (600 mg/d, approximately equivalent to 300 mg of aspirin) or anticoagulation (INR 2.0–3.0) alone. The lower-risk patients were randomly assigned to receive triflusal alone, anticoagulation (INR 2.0–3.0) alone, or triflusal plus anticoagulation to an INR of 1.25 to 2.0. The group receiving combination therapy had a significantly lower risk of primary outcome events (thromboembolism plus cardiovascular death) than the group treated with anticoagulation alone in both risk groups. Rates of severe bleeding, including intracerebral hemorrhage, were lower in the combination therapy arm than in the anticoagulation-only arm, but this difference was not statistically significant. However, it should be noted that the differences in primary outcome resulted largely from outcomes that probably were not a result of thromboembolism and that the achieved INR levels were similar in the anticoagulation and combination therapy groups.

- Currently, there is no evidence that combining anticoagulation with an antiplatelet agent reduces the risk of stroke or myocardial infarction compared with anticoagulant therapy alone in AF patients, but there is clear evidence of increased bleeding risk [10]. Therefore, in general, aspirin should not be added to anticoagulation therapy for AF patients without compelling indications for antiplatelet therapy.

Combination antiplatelet therapy

- Presently there are few data regarding the efficacy of combining antiplatelet agents for stroke prevention in AF patients [12]. Available studies have examined the clinical impact of aspirin plus clopidogrel in AF patients. Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist. Clopidogrel selectively and irreversibly inhibits ADP-induced fibrinogen binding to its receptor on platelets, thereby affecting ADP-dependent activation of the glycoprotein IIb/IIIa complex, the major receptor for fibrinogen present on the platelet surface. The value of combination antiplatelet therapy for stroke prevention in patients with AF was assessed in two ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trials, ACTIVE-W [13] and ACTIVE-A [14.••].
- ACTIVE-W evaluated the safety and efficacy of the combination of clopidogrel and aspirin versus warfarin in AF patients with at least one risk factor for stroke. This study was stopped prematurely by the safety monitoring committee after 3371 patients were enrolled because of the clear superiority of warfarin (INR 2.0–3.0) over the antiplatelet combination (RR, 1.44; 95% CI, 1.18–1.76; P=0.0003). Random assignment to clopidogrel (75 mg once daily) plus aspirin

(75–100 mg/d) was associated with a significant increase in the primary outcome of stroke, myocardial infarction, non–central nervous system (CNS) systemic embolism, or death from vascular causes after a median follow-up of 1.3 years compared with assignment to warfarin (target INR 2.0–3.0; 5.6% vs 3.9%; RR, 1.44; 95% CI, 1.18–1.76). There was no significant difference in major bleeding between the two treatment groups (2.4% per year for those on clopidogrel plus aspirin vs 2.2% per year for those on warfarin; RR, 1.10; 95% CI, 0.83–1.45). A subgroup analysis of the results of this trial raised the hypothesis that most of the benefit of warfarin over the combination of aspirin and clopidogrel was in patients who were already taking and tolerating oral anticoagulant therapy (ie, had survived the warfarin stress test), compared with patients who were warfarin naïve and about to start warfarin. Patients who were already taking warfarin at study entry and were randomly assigned to continue oral anticoagulation therapy had a substantial reduction in vascular events compared with those on the combination of clopidogrel and aspirin (3.7% vs 5.5% per year; RR, 0.67; 95% CI, 0.55–0.84) and a significantly lower risk of major bleeding (2.0% vs 2.6% per year; RR, 0.77; 95% CI, 0.56–1.06). By contrast, patients who were not taking oral anticoagulants at study entry (ie, those who were warfarin naïve) and were randomly assigned to start oral anticoagulation had a similar rate of vascular events (4.7% vs 5.9% per year; RR, 0.79; 95% CI, 0.53–1.18) and a higher risk of major bleeding (2.9% vs 1.7% per year; RR, 1.69; 95% CI, 0.93–3.12) compared with those on the combination of clopidogrel and aspirin.

- ACTIVE-A followed an approach similar to that of ACTIVE-W but selected patients with AF for whom therapy with a vitamin K antagonist (VKA) was considered unsuitable. ACTIVE-A randomly assigned patients to receive clopidogrel plus aspirin or aspirin plus placebo. The reasons patients were not considered suitable for VKA therapy or enrollment in ACTIVE-W included the presence of a specific risk factor for bleeding (23%), a physician assessment that the patient was not an appropriate candidate (50%), and a patient preference not to receive a VKA (26%). After a median follow-up of 3.6 years, compared with aspirin alone, clopidogrel once daily plus aspirin was associated with a reduction in the primary outcome of stroke, myocardial infarction, non-CNS systemic embolism, or death from vascular causes (6.8% vs 7.6% per year; RR, 0.89; 95% CI, 0.81–0.98; $P=0.01$), mainly because of a reduction in the rate of stroke (2.4% vs 3.3% per year; RR, 0.72; 95% CI, 0.62–0.83; $P<0.001$) (Table 1, Table 2). The benefit of the combination in reducing major vascular events, however, was balanced by an increased risk of major hemorrhages (major vascular events decreased 0.8% per year, major hemorrhages increased 0.7% per year; RR, 0.97; 95% CI, 0.89–1.06; $P=0.54$). Major bleeding among patients assigned to receive clopidogrel plus aspirin versus those on aspirin alone was 2.0% versus

Table 2. Main outcomes of ACTIVE-A

		Treatment events Clopidogrel plus aspirin		Aspirin		Clopidogrel plus aspirin vs aspirin		
Outcomes	**Definition**	**Number**	**Rate/year**	**Number**	**Rate/year**	**Relative risk**	**95% CI**	***P*-value**
Primary	Composite	832	6.8	924	7.6	0.89	0.81–0.98	0.014
Secondary	Stroke	296	2.4	408	3.3	0.72	0.62–0.83	<0.001
	Myocardial infarction	90	0.7	115	0.9	0.78	0.59–1.03	0.08
	Vascular death	600	4.7	599	4.7	1.0	0.89–1.12	0.97
	Non-CNS embolism	54	0.4	56	0.4	0.96	0.66–1.40	0.84

ACTIVE-A—Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; CNS—central nervous system (*Adapted from* Stuart J. Connolly, MD; with permission)

1.3% per year (RR, 1.57; 95% CI, 1.29–1.92). Clopidogrel plus aspirin reduced the risk of stroke by 28% but increased the risk of major extracranial hemorrhage by 51% (affecting predominantly the gastrointestinal tract) and major intracranial hemorrhage by 87% (Table 1).

Direct thrombin inhibitors

- Ximelagatran, a direct thrombin inhibitor, was compared with dose-adjusted warfarin in two major randomized controlled trials. In pooled analyses of both trials [10], the rate of main events (combined ischemic stroke, hemorrhagic stroke, and systemic embolic event) was similar in the ximelagatran and warfarin groups (1.62% vs 1.65% per year). Conflated rates of minor and major bleeding were lower with ximelagatran (31.7% vs 38.7% per year; $P<0.0001$), but serum alanine aminotransferase values rose transiently to more than three times the normal level in the subjects on ximelagatran (6.1% vs 0.8%; $P<0.0001$). Although these increases usually are reversible, they led the US Food and Drug Administration (FDA) to decide against approving ximelagatran for stroke prevention.
- Dabigatran etexilate is a prodrug given orally in a fixed dose and quickly converted by cytochrome P-450–independent esterases to dabigatran, a powerful reversible direct competitive inhibitor of thrombin with a prompt onset of action, consistent anticoagulant effect, and half-life of 12 to 17 h. RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy), a prospective, open-label, randomized trial with blinded assessment of all outcomes, investigated whether dabigatran is noninferior to warfarin. [15.••]. More than 18,000 patients with nonvalvular AF and at least one risk factor for stroke were randomly assigned to receive fixed doses of dabigatran (110 or 150 mg twice daily) or open-label, adjusted-dose warfarin (INR 2.0–3.0). After 2 years, the rates of systemic embolism or stroke

were similar among patients who received 110 mg dabigatran (1.53% per year) and those who received warfarin (1.69% per year; HR, 0.91; 95% CI, 0.74–1.11; $P<0.001$) and lower among patients who received dabigatran, 150 mg twice daily (1.11% per year; HR, 0.66; 95% CI, 0.53–0.82). Compared with warfarin (3.36% per year), the yearly rate of major bleeding was lower among patients who received 110 mg dabigatran (2.71% per year; RR, 0.80; 95% CI, 0.69–0.93) but similar among those assigned 150 mg dabigatran (3.11% per year; RR, 0.93; 95% CI, 0.81–1.07). Compared with warfarin taken once daily, dabigatran is given twice daily, but the level of anticoagulation does not need to be monitored. Other drugs may interact with dabigatran, and its effects may not be reversed readily in patients with bleeding complications.

Factor Xa inhibitors

- Idraparinux is an analogue of the heparin pentasaccharide that binds irreversibly to antithrombin and stimulates a change leading to inactivation of activated factor X. It has a half-life of 80 to 130 h and is given by subcutaneous injection once weekly. Compared with warfarin, idraparinux has been associated with substantially higher bleeding rates [16.•]. A clinical trial that randomly assigned 4576 AF patients to receive subcutaneous idraparinux (2.5 mg/wk) or adjusted-dose VKA therapy (target INR 2.0–3.0) had to be stopped after a mean follow-up of 11 months because of excess major bleeding among patients assigned to idraparinux versus VKA therapy (19.7 vs 11.3 events per 100 patient-years; HR, 1.74; 95% CI, 1.47–2.06). Older patients and those with renal insufficiency were at greater risk for such complications. There was no difference in the rate of stroke and systemic embolism (0.9 vs 1.3 events per 100 patient-years; HR, 0.71; 95% CI, 0.39–1.30; $P=0.007$ for noninferiority) or death (3.2 vs 2.9 deaths per 100 patient-years; $P=0.49$) between patients on idraparinux and those receiving VKA therapy. Several oral and subcutaneous factor Xa inhibitors currently are undergoing clinical evaluation.

Current guidelines

- Guidelines from the American Heart Association/American Stroke Association [3] and the American College of Chest Physicians [17.•] have not yet been updated to reflect the results of the ACTIVE-A and RE-LY trials but include the following:
  - Initiate oral anticoagulation within 2 weeks of an ischemic stroke or transient ischemic attack (TIA); however, for patients with large infarcts, hemorrhagic transformation, or uncontrolled hypertension, further delays may be appropriate.

- For patients with AF who suffer an ischemic stroke or TIA despite therapeutic anticoagulation, there are no data indicating that either increasing the intensity of anticoagulation or adding an antiplatelet agent provides additional protection against future ischemic events. In addition, both these strategies are associated with an increase in bleeding risk.
- Initiate warfarin for patients with AF and a moderate to high risk of stroke, such as those with a) mitral stenosis or a prosthetic heart valve, b) a history of prior ischemic stroke or systemic embolism, or c) two or more thromboembolic risk factors.
- In patients with AF, including those with paroxysmal AF, with only one major risk factor, initiate long-term antithrombotic therapy either as anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0–3.0), or as aspirin, at a dose of 75 to 325 mg/d. For patients at intermediate risk for ischemic stroke, a VKA, rather than aspirin, is recommended.
- In patients with AF, including those with paroxysmal AF, aged 75 years or older with no major risk factors, initiate long-term aspirin therapy at a dose of 75 to 325 mg/d because of their low risk of ischemic stroke.

FDA-approved treatments

Pharmacologic treatment

- The current FDA-approved pharmacologic therapies for stroke prevention in patients with AF include dose-adjusted warfarin (targeted to INR 2.0–3.0) and antiplatelet agents, as discussed earlier [18, 19]. The only antiplatelet agents discussed in this section are aspirin and clopidogrel, as these are the two antiplatelets shown to reduce the rate of stroke in patients with AF.

Antiplatelet agents

Aspirin

Standard dosage	75 to 325 mg/d orally.
Contraindications	Hypersensitivity to nonsteroidal anti-inflammatory drugs;children and teenagers with chickenpox or flu symptoms (risk of Reye's syndrome); syndrome of asthma, rhinitis, and nasal polyps.
Main drug interactions	Ketorolac, citalopram, desvenlafaxine, dicumarol, duloxetine, eptifibatide, escitalopram, fluoxetine, fluvoxamine, ginkgo, heparin, ketoprofen, methotrexate, nefazodone, paroxetine, sertraline, ticlopidine, varicella virus vaccine, venlafaxine, warfarin.
Main side effects	Gastrointestinal ulcers, bleeding, tinnitus, bronchospasm, angioedema, Reye's syndrome.

Special points	Patients should take aspirin with an 8-oz glass of water or food or milk. This drug should not be used in children because of the risk of Reye's syndrome. It should never be used in children and teenagers with chickenpox or flu symptoms.
Cost/cost-effectiveness	325-mg tablets (1 bottle, 100 each): $11.99; 81-mg enteric coated tablets (1000 each): $46.00: 975-mg enteric coated tablets (90 each): $11.25; 325-mg enteric coated tablets (14 bottles, 100 each): $46.06.

Clopidogrel

Standard dosage	75 mg/d orally.
Contraindications	Active bleeding (eg, peptic ulcer or intracranial hemorrhage; hypersensitivity to clopidogrel.
Main drug interactions	Abciximab, recombinant alteplase, argatroban, cilostazol, cimetidine, citalopram, dalteparin, desvenlafaxine, dicumarol, duloxetine, enoxaparin, eptifibatide, escitalopram, felbamate, fluconazole, fluoxetine, fluvoxamine, fondaparinux, heparin, ketoconazole, lansoprazole, nefazodone, omeprazole, pantoprazole, paroxetine, recombinant reteplase, sertraline, streptokinase, ticlopidine, urokinase, venlafaxine, voriconazole, warfarin.
Main side effects	Chest pain, hypertension, pruritus, purpuric disorder, rash, hypercholesterolemia, abdominal pain, constipation, gastritis, indigestion, epistaxis, purpura, arthralgia, backache, headache.
Special points	There have been reports of thrombotic thrombocytopenic purpura after exposure to clopidogrel.
Cost/cost-effectiveness	75-mg tablets (30 each): $155.99.

Oral anticoagulation

Warfarin

Standard dosage	Initially, 2 to 5 mg/d orally; adjust dosage based on the INR.
Contraindications	Threatened abortion; eclampsia; preeclampsia; alcoholism; major regional or lumbar anesthesia; cerebral aneurysms; dissecting aortic aneurysms; bacterial endocarditis; bleeding tendencies of the gastrointestinal, genitourinary, or respiratory tract; blood dyscrasias; cerebrovascular hemorrhage; gastrointestinal, genitourinary, or respiratory tract ulcerations or overt bleeding; hypersensitivity to warfarin; inadequate laboratory facilities; malignant hypertension; pericarditis and pericardial effusion; pregnancy; lack of patient cooperation; spinal puncture and other procedures with potential for uncontrollable bleeding; recent or potential surgery of the CNS or eye; recent or potential traumatic surgery resulting in a large open surface.
Main drug interactions	Abciximab, recombinant alteplase, amiodarone, aspirin, carboplatin, celecoxib, chamomile, cilostazol, citalopram, clopidogrel, cyclophosphamide, dalteparin, desvenlafaxine, dicumarol, doxorubicin, duloxetine, enoxaparin, eptifibatide, escitalopram, etoposide, fenofibrate, fish oil, fluconazole, fluorouracil, fluoxetine, fluvoxamine, fondaparinux, garlic, ginkgo, heparin, influenza virus vaccine, ketoprofen, levofloxacin, marijuana, methotrexate, metronidazole, moxifloxacin, naproxen, papaya, paroxetine, pomegranate,

	procarbazine, recombinant reteplase, ropinirole, sertraline, simvastatin, St. John's wort, streptokinase, sulfamethoxazole, testosterone, urokinase, venlafaxine, vincristine, voriconazole.
Main side effects	Cholesterol embolus syndrome, tissue necrosis, hemorrhage, hypersensitivity reaction (infrequent), intraocular hemorrhage.
Special points	Warfarin may cause major or fatal bleeding. Risk factors for bleeding include a high intensity of anticoagulation (INR >4.0), age≥65 years, highly variable INRs, a history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and a long duration of warfarin therapy. Regular monitoring of INR is necessary. There are multiple significant drug–drug interactions. Patients should avoid alcohol, cranberry juice, and eating large amounts of food high in vitamin K.
Cost/cost-effectiveness	1-mg tablets (30 each): $13.99; 2-mg tablets (30 each): $14.88; 2.5-mg tablets (30 each): $14.99; 3-mg tablets (30 each): $15.99; 4-mg tablets (30 each): $14.99; 5-mg tablets (30 each): $13.99; 7.5-mg tablets (30 each): $23.21; 10-mg tablets (30 each): $24.24.

Acknowledgements

Dr. Ovbiagele received support from the University of California, Los Angeles, Resource Centers for Minority Aging Research, Center for Health Improvement of Minority Elderly (RCMAR/CHIME) under National Institutes of Health/National Institute on Aging grant P30-AG021684.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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This was the first randomized controlled trial to study the efficacy of combination antiplatelet therapy versus single antiplatelet treatment in nonvalvular AF patients who are not candidates for warfarin therapy. Dual antiplatelet therapy was more efficacious in preventing incident vascular events, particularly stroke, but at the price of significantly more major bleeding.

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This randomized clinical trial evaluated the use of the direct thrombin inhibitor dabigatran compared with the gold standard, VKA therapy. Dabigatran appears to be a very promising alternative therapy to warfarin and may receive future regulatory approval for treatment of AF based on these results

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These are the most recently published expert consensus guidelines on the appropriate use of antithrombotic therapy to prevent stroke in patients with AF

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